UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,927	09/29/2003	Payman Amiri	18773.004	2378

27476 7590 11/15/2005

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
KANTAMNENI, SHOBHA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,927	AMIRI ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-86* is/are pending in the application.

4a) Of the above claim(s) *1-73 and 85* is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *74-84 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/04/05,04/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-86 are pending in this Application.

Election/Restrictions

Claims 1-73, and 85 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

Applicant's election without traverse the claims of Group VII, Claims 74-84 and 86, drawn to methods of using the products wherein X1 and X2 are each =N or NR4 in the reply filed on 08/14/05 is acknowledged.

The election requirement is made FINAL.

Upon further consideration by the examiner the species election requirement is herein withdrawn.

Claims 74-84, and 86 are examined herein as they read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 86 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 86 is rejected, as they provide the use of compound of claims 1, 16, 30, 44, or 58 in the manufacture of a medicament for the treatment of cancer, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 86 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 86 is examined as the method of use claims for the treatment of cancer, and the following rejections are made.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-84, and 86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling the instant compounds represented by formulas (I) to (V) for treating some particular/specific cancer disorders, **does not reasonably provide enablement for the treating any cancer disorder in general** by inhibiting Raf kinase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all cancers are treatable by using various chemotherapeutic agents and with compounds described in the method claims 18, and 19.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating a cancer disorder in a human or animal subject, comprising administering a composition comprising a compound represented by formulas (I) to (V). The nature of the invention is complex in that it encompasses the treatment of **any type of cancers**.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of **any number of cancers** comprising administering a composition comprising a compound represented by formulas (I) to (V). What's more, the scope of the compounds claimed to be useful for the treatment of cancer is extremely broad. The instant claims are deemed very broad since these claims read on a method of treatment of any cancer by inhibiting Raf kinase activity.

(3). Guidance of the Specification / (4). Working Examples::

The specification does not provide any guidance as to how one would administer the claimed compositions comprising instant compounds to a subject and treat **any** type of cancer cell. All of the guidance provided by the specification is directed towards the synthesis of the compounds represented by formula (I) to (V).

Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification discloses on page 309 "Using the procedures of Examples 1116 or 1117, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 50 μM." However,

the Examples 1116 or 1117 are procedures for the synthesis of the compounds and not the procedures for determining the raf kinase inhibitory activity.

(5). State of the Art:

While the state of the art is relatively high with regard to treating specific cancers, the state of the art with regard to treating **any cancer disorder** generally is underdeveloped. In particular, there is no known anticancer agent which is effective against all cancers. Carter, et al. (Chemotherapy of Cancer, 2nd ed., 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-I), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an

agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

(6). Predictability of the Art:

The invention is directed to treatment of cancer in general. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer could not be necessarily the same for the other type.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not the compound is effective for inhibiting cancer cells. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. In order to practice Applicant's invention, it would be

necessary for one to conduct the preceding experimentation for each type of cancer because, as described by Carter, et al., there is no known drug effective for inhibiting all types of cancer. Therefore, it would require **undue, unpredictable experimentation** to practice the claimed invention to treat **any** cancer disorder in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (I) to (V).

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for treating a **cancer in general** by administering the various compounds represented by formulas (I) to (V) is not considered to be enabled by the instant specification.

Claims 76, 80, and 83 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for specific agent selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, imatinib, specific anthracyclines, rituximab, trastuzumab for the treatment of specific cancer disorder, **does not reasonably provide enablement for the method of treating cancer in a human or animal subject** comprising administering a compound represented by formulas (I) to (V), and **agents in general**. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention **commensurate in scope** with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating a cancer disorder in a human or animal comprising administering a composition comprising a compound represented by formulas (I) to (V), and **any agent** for treating cancer. The nature of the invention is complex in that it encompasses the treatment of cancer comprising administering a compound represented by formulas (I) to (V) with a wide array of **various agents.**

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of any cancer by

administering a composition comprising a compound of claims 1, 16, 30, 44, or 58 with **any** agent for treatment of cancer.

(3). Guidance of the Specification / (4) Working Examples:

There is no guidance given by the specification as to what type of formulations comprising a compound of claims 1, 16, 30, 44, or 58 and an agent would be effective for the treatment of cancer. Pages 8-9 of the specification describes **agents** that can be used in combination with a composition comprising a compound represented by formulas (I) to (V) broadly as any suitable anticancer agents such as agents that induce apoptosis; polynucleotides; alkylating agents etc.

(5). State of the Art:

While the state of the art is relatively high with regard to specific anti-cancer agent, the state of the art with regard to anti-cancer agents in **general** is underdeveloped. Different agents have different chemical structures and are expected to behave in different manners. The level of skill in this art is low relative to the difficulty of the task of determining a composition comprising instant compound in combination with a suitable anti-cancer agent for the treatment of cancer.

(6). Predictabilitv of the Art:

The invention is directed to **agents in general**. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Chemotherapeutic agents are especially unpredictable due to their complex nature.

It is further noted that the pharmaceutical art is **unpredictable**, requiring each embodiment to be individually assessed for physiological activity. In the instant case, the claimed invention is highly **unpredictable**. For example anti-cancer agents such as 5-Fluorouracil, Gemcitabine, etoposide, doxorubicin, Cisplatin etc. have very different structures and thus will possess different properties such as binding affinities, solubilities etc. Thus one skilled in the art would recognize that the combination of these anti-cancer agents with instant compound represented by formulas (I) to (V) is highly unpredictable with regards to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions. One of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many agents having the claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the instant claimed invention is **highly unpredictable**.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of specific agent with a compound of instant claims 1, 16, 30, 44, or 58, pharmaceutical carrier, a dosage for each chemotherapeutic agent, the duration of treatment, route of treatment, etc. One would then need to test the combination in the model system to determine whether or not the combination is effective for inhibiting cancer cells and one would need to test for side effects and

toxicity. If the treatment is unsuccessful, one of skill in the art would have to modify the first combination with another chemotherapeutic agent, dosage, duration of treatment, route of administration, and sequence of administration etc. Even if successful, however, one of skill in the art would then need to determine the magnitude of the side effects and toxicity of utilizing a compound of instant claims 1, 16, 30, 44, or 58 in combination with the agent. One would then need to determine whether or not the magnitude of the side effects could be reduced by increasing or decreasing the dosage of one or both of the agents while retaining the functional aspect of the combination. Once the functionality to toxicity ratio was maximized, one would need to determine whether or not the combination which had been used was of sufficient benefit that it would serve as a useful conditioning combination. If not, one would need to select another agent and repeat the process until a sufficient benefit to detriment ratio had been achieved.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 74 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim 74. Applicant merely recites on page 309 of the specification "Using the procedures of Examples 1116 or 1117, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC50 of less than 5 μM" . However, the Examples 1116 or 1117 are the procedures for the synthesis of compounds, and not the procedures for testing the raf kinase inhibitory activity. Therefore, applicants generic claim are deemed to be beyond the scope of the enabled disclosure in the specification.

Note that "inhibiting Raf kinase activity in a human or animal subject" merely recited a mere mechanism of actions; thus the specifically therapeutic goals or the specifically therapeutic treatments of the claimed method herein for goals or the specifically therapeutic treatments of the claimed method herein for the mere mechanism of actions are lacking or missing.

Further, the recitation, "inhibiting Raf kinase activity in a human or animal subject" reads on merely the mechanism of action, not treating specific and particular pathological conditions.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni
Patent Examiner
Art Unit 1617

10/28/05

SHAOJIA A. JIANG, PH.D.
PRIMARY EXAMINER